# Erythrocyte fatty acids and risk of proliferative and nonproliferative fibrocystic disease in women in Shanghai, China<sup>1-3</sup>

Jackilen Shannon, Irena B King, Johanna W Lampe, Dao Li Gao, Roberta M Ray, Ming-Gang Lin, Helge Stalsberg, and David B Thomas

#### **ABSTRACT**

**Background:** Although benign breast changes are more common than breast cancer, little evidence regarding risk factors for benign breast conditions is available. Omega-3 (n-3) fatty acids have anti-inflammatory and antiproliferative actions and may be important in reducing the risk of benign conditions. There is a lack of research on the association of n-3 fatty acids with risk of benign fibrocystic breast changes.

**Objectives:** The objectives of the study were to evaluate the role of n-3 and other fatty acids in the development of benign proliferative fibrocystic conditions (PFCs) and nonproliferative fibrocystic conditions (NPFCs) in the breast and to evaluate the progression of fibrocystic changes in breast cancer.

**Design:** We conducted a case-control study to determine erythrocyte fatty acid concentrations in 155 women with NPFCs, 185 women with PFCs, 241 women with breast cancer (127 with non-proliferative and 114 with proliferative changes in the noncancerous extratumoral mammary epithelium), and 1030 control subjects. We estimated the relative risk of NPFCs, PFCs, and breast cancer with proliferative and nonproliferative changes in extratumoral tissue compared with the risk of these changes alone.

**Results:** Women in the highest quartile of eicosapentaenoic acid concentrations were 67% less likely to have an NPFC alone or with breast cancer and 49% less likely to have breast cancer than were women with PFCs.  $\gamma$ -Linolenic acid (18:3n–6) was positively associated with all fibrocystic and cancerous conditions. Palmitic: palmitoleic acid (n–7 saturation index) was inversely associated with risk in all comparisons.

**Conclusion:** Our results support a protective effects of n–3 fatty acid intake and the n–7 saturation index against benign fibrocystic breast changes and the progression of proliferative changes to breast cancer. *Am J Clin Nutr* 2009;89:265–76.

## INTRODUCTION

Fibrocystic breast conditions are relatively common among women, particularly premenopausal women between the ages of 20 and 50 y. Chart review studies indicate that  $\approx$ 60% of women referred for evaluation of breast symptoms receive a diagnosis of a benign condition (1). Of these benign conditions, fibrocystic changes are the most common, and between 30% and 70% of these lesions show evidence of epithelial hyperplasia or proliferation (2, 3). Although nonproliferative fibrocystic conditions (NPFCs) have been associated with little or no increase in breast

cancer risk (0–2%), proliferative fibrocystic conditions (PFCs) have been associated with a 1.5- to 4-fold increased risk of breast cancer, with the greatest increase in women with atypia (3). Benign breast conditions affect a large number of women and result in additional screening, an increased risk of breast cancer, and often pain and discomfort. However, the risk factors for these conditions remain poorly characterized. The few studies of diet and risk of NPFCs or PFCs have reported inconsistent results (4–9).

Fat intake and, to some extent, type of fat have been investigated as risk factors for benign breast conditions, but the findings have been inconsistent. None of the larger questionnairebased studies have considered specific types of polyunsaturated fatty acids (PUFAs; n-3 or n-6). In 3 studies of the comparison of fatty acid concentrations in breast adipose tissue between women with breast cancer and women with benign conditions, 2 reported significantly lower concentrations of n-3 fatty acids (10, 11) and 1 reported significantly higher concentrations of n-6 fatty acids in the tissue of women with breast cancer (12) than in women with benign conditions (10-13). In a study of subcutaneous fatty acid concentrations in women with breast cancer and control subjects with benign breast disease (BBD), no association was found with any of the fatty acids evaluated, including long-chain n-3 and n-6 fatty acids (13). None of these studies compared women with invasive disease directly with women with well-characterized fibrocystic conditions and control subjects.

It is hypothesized that breast cancer results from genetic alterations that cause morphologic changes that constitute an

<sup>&</sup>lt;sup>1</sup> From the Center for Research on Occupational and Environmental Toxicology, Oregon Health and Science University, Portland, OR (JS); the Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA (IBK, JWL, RMR, M-GL, and DBT); the Department of Epidemiology, Zhong Shan Hospital Cancer Center, Shanghai, China (DLG); and the Institute of Medical Biology, University of Tromsø, Tromsø, Norway (HS).

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<sup>&</sup>lt;sup>3</sup> Reprints not available. Address correspondence to J Shannon, Center for Research on Occupational and Environmental Toxicology, Oregon Health and Science University, 3181 Southwest Sam Jackson Park Road, L606, Portland, OR 97239. E-mail: shannoja@ohsu.edu.

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apparently continuous spectrum from normal to invasive malignancy through various grades of proliferative changes and atypia. If we accept this hypothesis, risk factors for invasive breast cancer could operate either before or after the development of hyperplasia. Those acting before the development of hyperplasia would be observed in relation to both PFCs and breast cancer, whereas those acting to enhance the probability that the PFC becomes breast cancer would be observed only in relation to breast cancer.

In the current study, we evaluated possible associations between erythrocyte fatty acids and risks of nonproliferative and proliferative fibrocystic changes. We also estimated risks of breast cancer relative to risks of fibrocystic changes by directly comparing women with breast cancer and concurrent nonproliferative and proliferative changes in their extratumoral epithelium with women with these conditions who had not developed breast cancer. Specifically, we hypothesized that long-chain n-3 and n-6 fatty acids, specifically common saturated and monounsaturated fatty acids, and, importantly, the ratios of these fatty acids would be associated with risk of fibrocystic changes and breast cancer.

## SUBJECTS AND METHODS

#### Study subjects

Study subjects were selected from participants in a previously described randomized trial of breast self-examination (BSE) in Shanghai, China (14). Trial participants were women who were born between 1925 and 1958, permanent residents of Shanghai, and either current or retired employees of the Shanghai Textile Industry Bureau. Between 1989 and 1991, all women in the cohort received a baseline questionnaire to collect information on their major demographic and reproductive risk factors for breast cancer. All women were actively monitored through July 2000 for benign breast changes and breast cancer. From 1995 through July 2000, 1429 women had breast lumps that were evaluated histologically at 1 of the 3 major hospitals affiliated with the Shanghai Textile Industry Bureau. A total of 622 women with fibrocystic changes and 432 with breast cancer had their conditions detected at these facilities during this study period. An attempt was made to administer a food-frequency questionnaire and a risk factor questionnaire to each woman to collect information on dietary intake, demographic characteristics, reproductive and gynecologic history, smoking and alcohol habits, medical history, family history of breast cancer, and occupational and recreational physical activity before breast

As shown in **Figure 1**, in-person interviews were completed for 551 of the women with fibrocystic changes, and 340 of these women had sufficient tissue for pathologic review and a satisfactory blood sample for analysis of erythrocyte fatty acids. Of the women with diagnosed fibrocystic changes and an adequate blood sample, 155 were characterized as having NPFCs and 185 had PFCs. Breast cancer was confirmed in 432 women; 336 of these women completed a food-frequency questionnaire and a detailed risk factor questionnaire and provided a blood sample. Six of these women were excluded because of a prior history of breast cancer, and 8 were excluded because their blood sample

was not adequate for fatty acid analyses; a final sample of 322 breast cancer cases was included in the present study. Of the 322 breast cancer cases, 241 had satisfactory noncancerous mammary epithelial tissue for histologic evaluation. After evaluation of the extratumoral tissue, as described below, 114 women were characterized as having breast cancer with proliferative extratumoral changes, and 127 were characterized as having breast cancer with nonproliferative extratumoral changes.

Control women were randomly selected from unaffected women in the BSE trial with no breast biopsy and were stratified by the age distribution of the women undergoing biopsy (Figure 2). A single control group was selected for studies of breast cancer and for concurrent studies of benign breast conditions. For each benign and malignant case enrolled between September 1995 and August 1997, 20 potential control subjects of the same age were randomly selected and listed. Potential control subjects were contacted, starting with the first 2 names on the list, until 2 women of the same age and menstrual status as their matched case were recruited. A total of 367 controls were recruited in this manner (64% of the eligible women contacted). Control subjects for cases who were enrolled between September 1997 and August 2000 were frequency-matched to the cases by 5-y age groups and hospital affiliation of their Shanghai Textile Industry Bureau factory at baseline. In-person interviews were completed for 704 (82%) of 862 control subjects selected in this manner. A total number of 1071 control subjects were recruited. Of these control subjects, 1 was excluded because of a calculated daily energy intake of >4000 kcal that was considered unreliable, 32 did not provide a blood sample, and 8 provided blood samples that were inadequate for fatty acid analyses, which yielded a total of 1030 control subjects for inclusion in the present analyses. In the statistical analyses for the present report, the individual matching on age and menstrual status was not retained. Women with fibrocystic conditions were compared with all interviewed control subjects from both studies, and the breast cancer cases were compared with the women with fibrocystic conditions. Comparisons of breast cancer cases with control subjects were reported previously (15).

Before enrollment, informed consent was obtained from each woman. The Institutional Review Board of the Fred Hutchinson Cancer Research Center and the Station for Prevention and Treatment of Cancer of the Shanghai Textile Industry Bureau approved the study in accordance with guidelines of the Office for Human Research Protections of the US Department of Health and Human Services.

Blood specimens were processed within  $\leq 5$  h of collection, and washed erythrocyte aliquots were stored in a  $-70^{\circ}$ C freezer until shipped by air to Seattle on dry ice. Blood was stored at the Fred Hutchinson Cancer Research Center at  $-70^{\circ}$ C.

#### Diagnosis and histologic classification

A single study pathologist (M-GL) reviewed slides of the samples from subjects with benign fibrocystic conditions and the extratumoral tissue from cancer cases and classified them according to the method developed by Aaman et al (16). The following features were scored on a scale of 0–3 (normal/not present, mild, moderate, or florid): adenosis, sclerosing adenosis, ductal hyperplasia, apocrine metaplasia, apocrine hyperplasia,

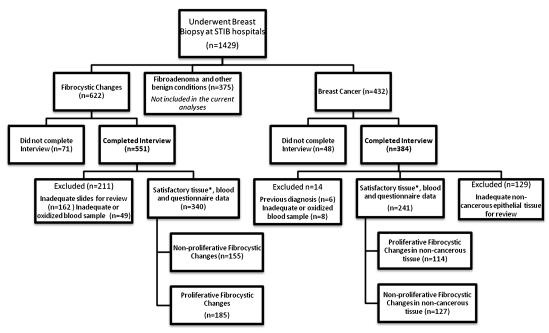


FIGURE 1. Recruitment of breast cancer and fibrocystic disease cases. STIB, Shanghai Textile Industry Bureau. \*At least 5 scanning power fields.

cysts, fibrosis, calcification, duct ectasia, inflammatory reaction, and lactation change. For lobular atypia, ductal atypia, and apocrine atypia, another scoring system was applied: 0 = none, 1 = uncertain, and 2 = atypical hyperplasia.

Samples of the major types of benign breast conditions and the extratumoral tissues of malignant cases were analyzed by H Stalsberg. There was satisfactory concordance between analyses by the 2 pathologists on assessment of levels of proliferation and presence of atypia (weighted  $\kappa$  coefficient: 0.4) but poor agreement on the detailed features of hyperplasia. Thus, we classified benign breast conditions and the noncancerous breast tissue from the malignant cases into 1 of the following 3 categories for statistical analyses: nonproliferative conditions (grade 0 or 1 ductal hyperplasia or sclerosing adenosis), proliferative conditions without atypia (grade 2 or 3 ductal hyperplasia or sclerosing adenosis and grade 0 or 1 atypia), and atypical hyperplasia (atypical ductal hyperplasia, atypical lobular hyperplasia, and atypical apocrine epithelium with grade 2 atypia). For the statistical analyses it was necessary to group the categories of proliferative conditions with and without atypia because of the small number of women characterized as having a proliferative condition with atypia. The resultant classification was similar to that of Dupont and Page (2). In all instances, the diagnosis of the study pathologist was used.

## Red blood cell fatty acid analyses

Red blood cells (250  $\mu$ L) were mixed with an equivalent volume of distilled water, and lipids were extracted with 2-propanol and chloroform according to the method described by Rose and Oklander (17). Butylated hydroxytoluene (5 mg/100 mL 2-propanol) was added as an antioxidant. The lipid extract was

dissolved in 5 mL acetyl chloride reagent and processed according to the method described by Lepage and Roy (18). After *trans*-esterification, fatty acid methyl esters were recovered in hexane, dried under nitrogen (40°C), and redissolved in 80  $\mu$ L hexane for gas chromatography analysis.

Fatty acid methyl esters were injected in a split mode (1:50) and separated with the use of an SP 2560 capillary column (100 m  $\times$ 0.25 mm internal diameter, 0.20-μm film thickness; Supelco, Bellefonte, PA) on a gas chromatograph (model 5890B; Hewlett-Packard Co, Avondale, PA). The gas chromatograph system was equipped with a flame ionization detector, electronic pressure control, Chemstation software (Hewlett-Packard), and an automatic sampler (model HP7673; Hewlett-Packard). As part of quality control (QC) measures, the long-term precision of the erythrocyte fatty acid measurement was monitored with repeat analysis of an in-house erythrocyte QC pool, which was extracted in each batch of 23 study samples. The accuracy of the chromatographic system was monitored with the use of commercial standards (GLC-87, NIH-D, and NIH-F; NU-CHEK, Elysian, MN). The CVs in the QC pool for the major fatty acids > 5% were  $\le 2\%$ ; for minor fatty acids ranging between 0.2% and 5%, the CVs were  $\leq$ 9.8%. Forty fatty acids were measured, including the following: 14:0, 14:1, 15:0, 16:0,16: 1n-9t, 16:1n-7t, 16:1n-9c, 16:1n-7c, 17:0, 17:1n-9, 18:0, 18:1n-10:12t, 18:1n-9t, 18:1n-8t, 18:1n-7t, 18:1n-6t, 18:1n-9c, 18:1n-8c, 18:1n-5c, 18:2n-6tt, 18:2n-6ct, 18:2n-6tc, 18:2n-6cc, 20:0, 18:3n-6, 18:3n-3, 20:1n-9, 20:2n-6, 20:3n-6, 22:0, 20:3n-3, 20:4n-6, 22:1n-9, 22:2n-6, 20:5n-3, 24:0, 22:4n-6, 24:1n-9, 22:5n-3, and 22:6n-3. For the statistical analyses we only considered those fatty acids relating to our primary hypotheses. In addition, if the fatty acids were present in very small amounts they were not included in any modeling. The case-control status was unknown to laboratory personnel. Fatty

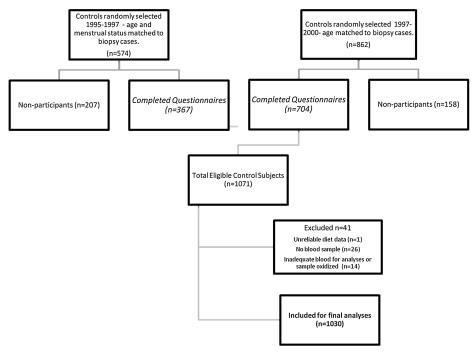


FIGURE 2. Recruitment of control subjects from the breast self-examination cohort from Shanghai, China.

acid composition was reported as the percentage by weight of the total fatty acids in the erythrocyte membrane.

#### Statistical analyses

The frequencies of demographic and reproductive characteristics in cases and control subjects were compared, and the percentages among the cases were standardized to the age distribution of control subjects by using indirect adjustment methods (19). Specific fatty acids were first evaluated as continuous variables. Differences in mean intakes across the group were evaluated by using a Satterwhite's t test for unequal variances. In addition to evaluating individual fatty acids, we also created meaningful ratios of fatty acids, including ratios of n-3 to n-6, of linoleic acid (LA; 18:2n–6) to γ-linolenic acid (GLA; 18:3n–6), and of GLA to arachidonic acid (AA; 20:4n-6) because GLA is an intermediary in the elongation of LA to AA and an n-7 and n-9 saturation index (SI). The SI represents ratios of the 2 most common saturated fatty acids in tissues and monounsaturated fatty acids that are direct metabolites of these saturated fatty acids. Fatty acid concentrations were categorized into quartiles on the basis of the distribution of fatty acid concentrations in the control women. To estimate the association between fatty acid concentrations and risk of NPFCs and PFCs, conditional logistic regression models were used to calculate odds ratios (ORs) and 95% CIs for risk of disease compared with no disease (20). In an effort to estimate the role of fatty acids in the development of breast cancer in women with BBD, we modeled the association between fatty acid concentration and risk of breast cancer compared with BBD separately for women with and without proliferative elements in their mammary epithelium. All statistical analyses were performed by using SAS/PC version 8.2

(SAS Institute, Cary, NC), and tests were considered statistically significant at P < 0.05. Because cases (either fibrocystic disease or breast cancer) and control subjects were not recruited and interviewed at an equal rate over the 5 y of data collection, case-control analyses (subjects with NPFCs compared with control subjects and subjects with PFCs compared with control subjects) were conditioned according to year of interview (1995–1996, 1997, 1998–1999, or 2000–2001). ORs for all models were adjusted for age according to 5-y age categories.

Potential confounding by other nondietary factors or by intervention arm of the main BSE trial was evaluated by conducting univariate analyses and then adding each variable found to be independently associated with breast cancer risk separately into the main model. Family history of breast cancer, age at menarche, age at first full-term pregnancy, age at first live birth, total live births, number of prior benign breast lumps, duration of oral contraceptive use, duration of intrauterine device use, number of induced abortions, menopausal status, years of breastfeeding, years since last induced abortion, frequency of BSE practice, education, smoking, alcohol use, body mass index, physical activity, and reported vitamin E intake were evaluated as possible confounders. Variables were considered to be confounders if they changed the estimated OR of the main independent variable (erythrocyte fatty acid) by  $\geq 10\%$ . For all but one of the models, none of these variables was found to be a confounder; therefore, only age was maintained as a covariate in the final models. For the comparison of women with breast cancer and proliferative extratumoral changes with women with PFCs alone, the number of induced abortions was determined to change the OR of the main independent variable by  $\geq 10\%$  and was maintained in the final model for this comparison. The significance of a trend in risk across erythrocyte fatty acid compositions was evaluated by

**TABLE 1**Selected characteristics of women with breast cancer, women with proliferative and nonproliferative extratumoral tissue, women with proliferative and nonproliferative fibrocystic changes alone, and control subjects in Shanghai, China<sup>I</sup>

Characteristic	Breast cancer			Fibrocystic changes			_
	All cases <sup>2</sup> $(n = 241)$	Proliferative <sup>2</sup> $(n = 114)$	Nonproliferative <sup>2</sup> $(n = 127)$	All fibrocystic disease <sup>2</sup> $(n = 340)$	Proliferative <sup>2</sup> $(n = 185)$	Nonproliferative <sup>2</sup> $(n = 155)$	Control subjects $(n = 1030)$
		n (%)			n (%)		n (%)
Age							
35–39 y	8 (3.3)	5 (4.4)	3 (2.4)	43 (12.7)	20 (10.8)	23 (14.8)	13 (1.3)
40–44 y	69 (28.6)	33 (29.0)	36 (28.4)	143 (42.1)	83 (44.9)	60 (38.7)	456 (44.3)
45–49 y	57 (23.7)	31 (27.2)	26 (20.5)	96 (28.2)	53 (28.7)	43 (27.7)	216 (21.0)
50–59 y	35 (14.5)	12 (10.5)	23 (18.1)	24 (7.1)	8 (4.3)	16 (10.3)	121 (11.8)
≥60 y	72 (29.9)	33 (29.0)	39 (30.7)	34 (10.0)	21 (11.4)	13 (8.4)	224 (21.8)
Education							
≤Elementary school	62 (19.1)	$24 (16.5)^3$	38 (21.3)	24 (14.0)	13 (12.9)	11 (16.3)	195 (18.9)
Middle school	161 (74.8)	$80 (74.7)^3$	81 (74.7)	296 (79.6)	163 (81.8)	133 (76.8)	805 (78.2)
≥College	18 (6.4)	$10 (8.9)^3$	8 (4.2)	20 (6.6)	9 (5.5)	11 (7.1)	29 (2.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)	0 (0.0)	1 (0.1)
BMI (in kg/m <sup>2</sup> )							
≤20	41 (17.7)	22 (18.8)	19 (16.7)	85 (21.0)	42 (22.2)	43 (23.8)	196 (19.0)
>20 to ≤25	143 (61.3)	67 (61.1)	76 (60.7)	197 (57.5)	108 (58.7)	89 (58.1)	602 (58.5)
>25	57 (21.3)	25 (20.3)	32 (22.8)	58 (17.2)	35 (19.1)	23 (18.3)	232 (22.5)
Physical activity (intensity of occupational and recreational activity)							
Light	61 (25.1)	30 (25.0)	31 (25.1)	90 (27.3)	46 (25.8)	44 (29.0)	184 (17.9)
Moderate	171 (71.7)	78 (70.3)	93 (73.4)	236 (69.2)	132 (71.4)	104 (66.5)	776 (75.3)
Heavy	9 (3.3)	6 (4.9)	3 (1.7)	14 (3.7)	7 (3.0)	7 (4.7)	70 (6.8)
Smoking history							
Nonsmoker	86 (32.2)	39 (28.4)	47 (34.1)	125 (39.6)	69 (42.2)	56 (35.3)	359 (34.9)
Lived with smoking partner							
1–15 y	69 (35.3)	33 (37.2)	36 (34.8)	114 (26.1)	65 (26.0)	49 (26.5)	289 (28.1)
16–20 y	37 (16.7)	18 (17.1)	19 (16.8)	68 (19.2)	36 (17.8)	32 (20.4)	217 (21.1)
>20 y	45 (14.2)	22 (15.9)	23 (12.7)	31 (14.4)	15 (14.1)	16 (16.4)	160 (15.5)
Unknown	4 (1.8)	2 (1.6)	2 (1.8)	2 (0.8))	0 (0.0)	2 (1.5)	5 (0.5)
Family history of breast cancer							
No	$228 (95.0)^3$	$109 (95.8)^3$	$119 (93.7)^3$	328 (96.6)	179 (96.3)	149 (97.4)	1013 (98.4)
Yes	$13 (5.3)^3$	$5(4.3)^3$	$8 (6.4)^3$	12 (3.5)	6 (3.9)	6 (2.8)	17 (1.6)

<sup>&</sup>lt;sup>1</sup> P values for age-adjusted model were stratified by year of interview (1995–1996, 1997, 1998–1999, and 2000–2001) by conditional logistic regression.

entering quartiles of the erythrocyte fatty acid proportions into the logistic model as different values of a single ordinal variable.

#### RESULTS

Dietary, demographic, and reproductive characteristics of the study subjects were reported previously (21–23). As shown in **Table 1**, women with breast cancer with proliferative extratumoral changes were significantly less educated than were control subjects; these women, women with breast cancer with nonproliferative extratumoral changes, and all breast cancer cases were significantly more likely than were control subjects to report having first-degree relatives with breast cancer. As shown in **Table 2**, women with PFCs reported fewer live births, were more likely to have never breastfed or breastfed <6 mo, and had significantly more breast lumps evaluated by a medical worker than did control subjects. In comparison with control subjects, women with breast cancer with proliferative extratumoral tissue also reported fewer live births; in addition, women

with breast cancer with nonproliferative extratumoral changes were significantly younger at menarche than were control subjects and were more likely to be postmenopausal than were women with NPFCs alone. The prevalence of cigarette smoking was low (<3%) among all women.

In **Table 3** we present results for risk in women with NPFCs alone and risk in women with breast cancer with non-proliferative extratumoral changes compared with control subjects and risk in women with breast cancer with nonproliferative changes compared with women with NPFCs alone. A greater percentage of palmitic and palmitoleic acids was associated with a significant increase in risk of both NPFCs and breast cancer with nonproliferative changes as compared with control subjects. GLA was significantly associated with an increased risk of breast cancer with nonproliferative changes as compared with that for either control subjects or for those with NPFCs alone, whereas vaccenic acid was associated with a significant increase in risk only for women with breast cancer with nonproliferative changes as compared with control subjects. Total n–3 PUFAs and eicosapentaenoic acid (EPA, 20:5n–3) were associated with

<sup>&</sup>lt;sup>2</sup> Indirect age-adjusted percentages based on age distribution of control subjects.

<sup>&</sup>lt;sup>3</sup> Significantly different from control subjects, P < 0.05.

TABLE 2
Selected reproductive characteristics of women with breast cancer, women with proliferative and nonproliferative extratumoral tissue, women with proliferative and nonproliferative fibrocystic changes alone, and control subjects in Shanghai, China<sup>1</sup>

Characteristic	Breast cancer cases			Fibrocystic changes			
	All cases <sup>2</sup> $(n = 241)$	Proliferative <sup>2</sup> $(n = 114)$	Nonproliferative <sup>2</sup> $(n = 127)$	All fibrocystic disease <sup>2</sup> $(n = 340)$	Proliferative <sup>2</sup> $(n = 185)$	Nonproliferative <sup>2</sup> $(n = 155)$	Control subjects $(n = 1030)$
		n (%)			n (%)		n (%)
Age at menarche							
≤13 y	42 (18.5)	15 (12.2)	$27(24.5)^3$	61 (14.4)	29 (14.5)	32 (15.1)	167 (16.2)
14 y	42 (19.5)	25 (24.4)	$17(13.3)^3$	84 (24.1)	52 (25.2)	32 (22.8)	199 (19.3)
15 y	58 (24.0)	23 (21.4)	$35(27.0)^3$	69 (20.4)	36 (18.3)	33 (20.8)	201 (19.5)
16 y	46 (17.9)	21 (14.9)	$25(20.5)^3$	61 (16.8)	30 (17.7)	31 (16.1)	214 (20.8)
≥17 y	53 (20.3)	30 (27.8)	$23(13.8)^3$	65 (24.5)	38 (24.5)	27 (25.5)	248 (24.1)
Missing							1 (0.10)
Number of live births							
None	$13 (4.8)^3$	$7(5.9)^3$	6 (4.2)	15 (4.0)	$9(4.0)^3$	6 (3.5)	37 (3.6)
1	$135 (65.8)^3$	$73 (70.9)^3$	62 (61.7)	269 (67.3)	$149 (68.6)^3$	120 (65.5)	696 (67.6)
2	$41 (13.8)^3$	9 (6.6) <sup>3</sup>	32 (19.4)	26 (11.4)	$13(13.3)^3$	13 (8.6)	118 (11.5)
≥3	$52 (15.9)^3$	$25 (16.8)^3$	27 (15.0)	28 (17.1))	$14 (14.3)^3$	14 (21.6)	175 (17.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (1.0)	4 (0.4)
Age at first live birth							
No live births	15 (5.4)	7 (5.9)	8 (5.3)	17 (4.4)	9 (4.0)	8 (4.5)	41 (3.6)
≤24 y	63 (20.2)	28 (20.2)	35 (19.7)	56 (27.3)	29 (24.2)	27 (12.5)	260 (25.2)
25–29 y	116 (53.6)	53 (50.1)	63 (56.8)	212 (57.9)	115 (58.1)	97 (57.5)	582 (56.5)
>30 y	47 (21.1)	26 (24.1)	21 (18.5)	55 (13.6)	32 (14.0)	23 (12.8)	147 (14.3)
Duration of breastfeeding	, ,		` '	· · ·		, ,	
Never breastfed	$51 (22.8)^3$	24 (22.65)	27 (24.1)	90 (23.7)	$52(23.4)^3$	38 (22.2)	221 (21.5)
<6 mo	$46(20.2)^3$	23 (20.3)	23 (20.4	93 (25.1)	$53(26.0)^3$	40 (25.5)	205 (19.9)
7–12 mo	$68 (32.3)^3$	39 (38.2)	29 (25.9)	106 (26.3)	$52(25.8)^3$	54 (26.0)	354 (34.4)
13-24 mo	$34 (12.2)^3$	5 (3.6)	29 (19.2)	26 (10.9)	$13(11.0)^3$	13 (11.7)	109 (10.6)
>25 mo	$42(12.8)^3$	23 (15.5)	19 (10.6)	25 (14.3)	$15(14.1)^3$	10 (14.9)	141 (13.7)
Duration of oral contraceptive use	` /	, ,	` '	` ,	, ,	. ,	` ,
Never used	213 (89.1)	101 (89.2)	112 (88.6)	301 (86.4)	168 (89.2)	133 (84.5)	941 (91.4)
≤1 y	15 (6.6)	7 (6.4)	8 (6.6)	19 (6.3)	9 (4.4)	10 (8.3)	33 (3.2)
_ √ >1 y	13 (4.5)	6 (4.6)	7 (5.0)	20 (7.5)	8 (6.6)	12 (14.3)	55 (5.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Number of induced abortions	` ′	` '	` '	` '	` /	. ,	` /
0	100 (39.9)	46 (40.6)	54 (39.7)	118 (31.9)	70 (35.7)	48 (28.6)	416 (40.4)
1	94 (39.5)	46 (38.2)	48 (39.8)	148 (46.6)	80 (46.7)	68 (48.1)	417 (40.5)
2	34 (16.1)	15 (15.5)	19 (16.5)	61 (18.1)	29 (16.5)	32 (19.8)	162 (15.7)
Missing	13 (4.8)	7 (5.9)	6 (4.2)	13 (3.5)	6 (3.0)	7 (3.7)	35 (3.4)
Number of breast lumps evaluated	()	. (2.5)	* ()	(0.0)	J (213)	. (21.)	()
by medical worker							
0	312 (93.0) <sup>3,4</sup>	105 (92.6)	120 (93.7)	299 (89.1)	$158 (86.4)^3$	141 (92.9)	999 (97.0)
1	$13 (4.8)^{3,4}$	8 (6.9)	3 (3.0)	26 (7.2)	$17 (9.1)^3$	9 (4.5)	21 (2.0)
>2	5 (2.3) <sup>3,4</sup>	1 (0.7)	4 (3.5)	15 (3.9)	$10(4.8)^3$	5 (2.8)	10 (1.0)
Menopause	- (2.0)	- (0)	. (5.5)	(5.7)	()	- (2.0)	(1.0)
No	131 (64.7)	69 (67.8)	62 (61.8) <sup>5</sup>	275 (66.8)	147 (65.6)	128 (68.8)	669 (65.0)
Yes	110 (35.5)	45 (32.4)	65 (38.3) <sup>5</sup>	65 (33.4)	38 (34.6)	27 (31.4)	361 (35.1)

<sup>&</sup>lt;sup>1</sup> P values for age-adjusted model were stratified by year of interview (1995–1996, 1997, 1998–1999, and 2000–2001) by conditional logistic regression.

a significant reduction in risk of NPFCs alone, whereas total n-3 PUFAs, EPA, and docosapentaenoic acid (22:5n-3) were associated with a significant reduction in risk of breast cancer in women with nonproliferative changes as compared with that in control subjects.

Results from models for risk of PFCs alone and breast cancer with proliferative changes compared with control subjects, breast cancer with proliferative changes compared with PFC,

and all breast cancer compared with PFC are presented in **Table 4**. The long-chain n-3 fatty acid EPA was significantly inversely associated with risk of all breast cancer as compared with PFCs, and a similar although nonsignificant trend was seen for breast cancer with proliferative changes as compared with PFCs. Conversely, GLA was associated with a significant increase in risk of all breast cancer; in addition, GLA and total n-6 fatty acids were associated with breast cancer with proliferative

<sup>&</sup>lt;sup>2</sup> Indirect age-adjusted percentages based on age distribution of controls.

<sup>&</sup>lt;sup>3</sup> Significantly different from control subjects, P < 0.05.

<sup>&</sup>lt;sup>4</sup> Significantly different from subjects with proliferative fibrocystic changes, P < 0.05.

<sup>&</sup>lt;sup>5</sup> Significantly different from subjects with nonproliferative fibrocystic changes, P < 0.05.

TABLE 3 Erythrocyte fatty acid concentrations among women in Shanghai, China, and risk of nonproliferative fibrocystic conditions (NPFCs) with or without breast cancer  $(BC)^I$ 

	Quartiles of erythrocyte fatty acid concentrations							
	1	2	3	4	P for trend			
	% of total by wt							
Palmitic acid (16:0)	$0 < n \le 18.16$	$18.16 < n \le 18.70$	$18.70 < n \le 19.27$	19.27 < n	_			
NPFCs alone vs control	1.00	$1.49 (0.70, 3.19)^2$	1.06 (0.49, 2.29)	2.43 (1.17, 5.05)	0.02			
NPFCs with BC vs control	1.00	1.13 (0.45, 2.84)	1.51 (0.64, 3.55)	2.62 (1.16, 5.93)	0.002			
NPFCs with BC vs NPFCs alone	1.00	0.62 (0.22, 1.72)	1.20 (0.45, 3.19)	1.10 (0.44, 2.77)	0.31			
Palmitoleic acid (16:1n-7)	$0 < n \le 0.13$	$0.13 < n \le 0.17$	$0.17 < n \le 0.24$	0.24 < n				
NPFCs alone vs control	1.00	1.36 (0.74, 2.53)	2.78 (1.49, 5.19)	2.35 (1.19, 4.64)	0.002			
NPFCs with BC vs control	1.00	1.34 (0.63, 2.83)	4.52 (2.22, 9.20)	4.29 (2.07, 8.85)	< 0.0001			
NPFCs with BC vs NPFCs alone	1.00	0.94 (0.40, 2.22)	1.40 (0.64, 3.09)	1.81 (0.79, 4.15)	0.07			
Oleic acid $(18:1n-9c)$	$0 < n \le 9.81$	$9.81 < n \le 10.38$	$10.38 < n \le 11.02$	11.02 < n	_			
NPFCs alone vs control	1.00	0.67 (0.39, 1.15)	0.59 (0.33, 1.08)	0.93 (0.47, 1.83)	0.36			
NPFCs with BC vs control	1.00	1.00 (0.56, 1.79)	1.12 (0.63, 2.02)	1.44 (0.73, 2.85)	0.32			
NPFCs with BC vs NPFCs alone	1.00	1.18 (0.62, 2.26)	1.70 (0.84, 3.45)	1.28 (0.58, 2.81)	0.27			
Vaccenic acid (18:1n-7)	$0 < n \le 0.85$	$0.85 < n \le 0.93$	$0.93 < n \le 1.01$	1.01 < n				
NPFCs alone vs control	1.00	1.35 (0.75, 2.45)	1.98 (1.06, 3.69)	1.27 (0.65, 2.49)	0.25			
NPFCs with BC vs control	1.00	1.54 (0.81, 2.91)	1.97 (1.04, 3.71)	2.49 (1.29, 4.79)	0.005			
NPFCs with BC vs NPFCs alone	1.00	0.93 (0.45, 1.95)	1.24 (0.59, 2.63)	1.49 (0.67, 3.31)	0.22			
n–6 PUFAs <sup>3</sup>	$0 < n \le 26.61$	26.61 < n < 27.76	27.76 < n < 29.48	29.48 < n	_			
NPFCs alone vs control	1.00	0.88 (0.50, 1.56)	1.24 (0.71, 2.18)	0.93 (0.45, 1.95)	0.71			
NPFCs with BC vs control	1.00	0.70 (0.40, 1.22)	0.57 (0.31, 1.04)	0.87 (0.44, 1.73)	0.35			
NPFCs with BC vs NPFCs alone	1.00	0.86 (0.44, 1.70)	0.57 (0.29, 1.15)	1.44 (0.61, 3.37)	0.91			
Linoleic acid (18:2)	$0 < n \le 10.19$	$10.19 < n \le 11.40$	$11.40 < n \le 13.63$	13.63 < n	_			
NPFCs alone vs control	1.00	0.75 (0.42, 1.32)	1.24 (0.70, 2.23)	0.78 (0.37, 1.64)	0.9			
NPFCs with BC vs control	1.00	0.67 (0.38, 1.17)	0.53 (0.28, 0.99)	0.83 (0.42, 1.66)	0.27			
NPFCs with BC vs NPFCs alone	1.00	1.35 (0.68, 2.68)	0.64 (0.31, 1.32)	1.28 (0.56, 2.95)	0.78			
$\gamma$ -Linolenic acid (18:3n–6)	0 < n < 0.05	0.05 < n < 0.07	$0.07 < n \le 0.09$	0.09 < n	-			
NPFCs alone vs control	1.00	0.75 (0.45, 1.26)	0.78 (0.39, 1.57)	1.05 (0.54, 2.05)	0.98			
NPFCs with BC vs control	1.00	0.87 (0.49, 1.53)	1.20 (0.59, 2.43)	1.78 (0.93, 3.38)	0.05			
NPFCs with BC vs NPFCs alone	1.00	1.14 (0.60, 2.18)	1.43 (0.63, 3.25)	2.24 (1.07, 4.67)	0.03			
Arachidonic acid (20:4)	$0 < n \le 11.43$	$11.43 < n \le 12.17$	$12.17 < n \le 12.92$	12.92 < n	—			
NPFCs alone vs control	1.00	0.79 (0.44, 1.45)	$0.89 \ (0.48, 1.63)$	0.78 (0.43, 1.44)	0.53			
NPFCs with BC vs control	1.00	0.69 (0.37, 1.27)	0.93 (0.51, 1.70)	0.69 (0.37, 1.29)	0.43			
NPFCs with BC vs NPFCs alone	1.00	0.94 (0.45, 1.94)	1.08 (0.54, 2.16)	0.81 (0.39, 1.66)	0.43			
n=3 PUFAs <sup>4</sup>	$0 < n \le 7.05$	$7.05 < n \le 7.64$	$7.64 < n \le 8.36$	8.36 < n	_			
NPFCs alone vs control	$0 < n \le 7.03$ $1.00$	$0.76 \ (0.41, 1.41)$	$0.72 \ (0.40, 1.30)$	0.52 (0.28, 0.96)	0.04			
NPFCs with BC vs control	1.00	0.52 (0.28, 0.96)	0.72 (0.40, 1.30)	0.49 (0.27, 0.90)	0.04			
NPFCs with BC vs NPFCs alone	1.00	0.52 (0.28, 0.90)	0.63 (0.31, 1.28)	0.49 (0.27, 0.90)	0.03			
Eicosapentaenoic acid (20:5)	$0 < n \le 0.46$	0.72 (0.33, 1.47) $0.46 < n \le 0.56$	$0.56 < n \le 0.69$	0.79 (0.39, 1.00) 0.69 < n	0.41			
NPFCs alone vs control	$0 < n \le 0.40$ $1.00$			0.09 < n 0.33 (0.18, 0.61)	< 0.0001			
	1.00	0.33 (0.18, 0.61)	0.25 (0.14, 0.47)					
NPFCs with BC vs control		1.22 (0.70, 2.13)	0.51 (0.28, 0.94)	0.33 (0.16, 0.66)	0.0002			
NPFCs with BC vs NPFCs alone	1.00	2.36 (1.21, 4.59)	2.00 (0.96, 4.16)	0.75 (0.33, 1.71)	0.82			
Docosapentaenoic acid (22:5)	$0 < n \le 1.62$	$1.62 < n \le 1.85$	$1.85 < n \le 2.09$	2.09 < n	0.57			
NPFCs alone vs control	1.00	0.83 (0.45, 1.54)	0.91 (0.48, 1.73)	0.79 (0.42, 1.52)	0.57			
NPFCs with BC vs control	1.00	0.54 (0.29, 1.00)	0.58 (0.31, 1.08)	0.37 (0.19, 0.74)	0.009			
NPFCs with BC vs NPFCs alone	1.00	0.88 (0.44, 1.77)	1.01 (0.49, 2.09)	0.53 (0.25, 1.11)	0.15			
Docosahexaenoic acid (22:6)	$0 < n \le 4.40$	$4.40 < n \le 4.90$	$4.90 < n \le 5.46$	5.46 < n				
NPFCs alone vs control	1.00	0.94 (0.50, 1.77)	0.97 (0.53, 1.76)	0.68 (0.36, 1.25)	0.24			
NPFCs with BC vs control	1.00	0.70 (0.38, 1.30)	0.67 (0.37, 1.22)	0.60 (0.33, 1.11)	0.11			
NPFCs with BC vs NPFCs alone	1.00	0.72 (0.34, 1.52)	0.55 (0.27, 1.12)	0.71 (0.35, 1.46)	0.26			

<sup>&</sup>lt;sup>1</sup> PUFAs, polyunsaturated fatty acids. Models stratified by year of interview (1995–1996, 1998–1999, and 2000–2001) and adjusted for age by conditional logistic regression. Number of subjects in age-adjusted model: 155 with NPFCs, 127 with NPFCs and BC, and 1030 controls.

<sup>&</sup>lt;sup>2</sup> Odds ratio and 95% CI (all such values).

 $<sup>^{3}</sup>$  18:2n-6cc + 18:3n-6 + 20:2n-6 + 20:3n-6 + 20:4n-6 + 22:2n-6 + 22:4n-6.

 $<sup>^{4}</sup>$  18:3n-3 + 20:3n-3 + 20:5n-3 + 22:5n-3 + 22:6n-3.

TABLE 4
Erythrocyte fatty acid concentrations among women in Shanghai, China, and risk of proliferative fibrocystic conditions (PFCs) with or without breast cancer (BC)<sup>I</sup>

	Quartiles of erythrocyte fatty acid concentrations					
	1	2	3	4	P for trend	
		· ·	otal by wt			
Palmitic acid (16:0)	$0 < n \le 18.16$	$18.16 < n \le 18.70$	$18.70 < n \le 19.27$	19.27 < n	_	
PFCs vs control	1.00	$0.94 (0.44, 2.03)^2$	0.67 (0.32, 1.47)	1.16 (0.55, 2.42)	0.64	
PFCs with BC vs control	1.00	0.52 (0.21, 1.30)	0.66 (0.28, 1.52)	1.19 (0.53, 2.64)	0.13	
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	0.57 (0.23, 1.45)	0.77 (0.32, 1.87)	0.87 (0.38, 1.98)	0.75	
All BCs vs PFCs alone	1.00	0.66 (0.31, 1.41)	1.02 (0.49, 2.08)	1.14 (0.58, 2.25)	0.22	
Palmitoleic acid (16:1n–7)	$0 < n \le 0.13$	$0.13 < n \le 0.17$	$0.17 < n \le 0.24$	0.24 < n	_	
PFCs alone vs control	1.00	1.91 (1.03, 3.55)	2.87 (1.50, 5.50)	2.87 (1.42, 5.80)	0.001	
PFCs with BC vs control	1.00	3.93 (1.63, 9.48)	8.76 (3.65, 21.0)	8.13 (3.21, 20.6)	< 0.0001	
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	2.62 (0.64, 4.12)	2.55 (1.02, 6.35)	1.97 (0.74, 5.24)	0.12	
All BCs vs PFCs alone	1.00	1.09 (0.55, 2.17)	1.76 (0.90, 3.44)	1.72 (0.84, 3.53)	0.04	
Oleic acid (18:1n–9c)	$0 < n \le 9.81$	$9.81 < n \le 10.38$	$10.38 < n \le 11.02$	11.02 < n	_	
PFCs alone vs control	1.00	1.01 (0.58, 1.76)	0.82 (0.46, 1.50)	1.67 (0.82, 3.42)	0.46	
PFCs with BC vs control	1.00	1.06 (0.59, 1.89)	0.69 (0.35, 1.37)	1.24 (0.60, 2.56)	0.98	
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	1.12 (0.59, 2.11)	0.86 (0.42, 1.78)	1.00 (0.46, 2.21)	0.85	
All BCs vs PFCs alone	1.00	1.01 (0.60, 1.70)	1.06 (0.60, 1.88)	0.99 (0.52, 1.90)	0.94	
Vaccenic acid (18:1n-7)	$0 < n \le 0.85$	$0.85 < n \le 0.93$	$0.93 < n \le 1.01$	1.01 < n	_	
PFCs alone vs control	1.00	1.40 (0.78, 2.48)	1.22 (0.65, 2.29)	1.09 (0.56, 2.14)	0.86	
PFCs with BC vs control	1.00	1.14 (0.61, 2.14)	1.16 (0.61, 2.20)	1.09 (0.54, 2.20)	0.76	
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	0.66 (0.33, 1.33)	0.98 (0.48, 2.00)	0.87 (0.39, 1.93)	0.97	
All BCs vs PFCs alone	1.00	0.85 (0.48, 1.52)	1.32 (0.73, 2.38)	1.24 (0.65, 2.37)	0.24	
n−6 PUFAs⁴	$0 < n \le 26.61$	26.61 < n < 27.76	27.76 < n < 29.48	29.48 < n	_	
PFCs alone vs control	1.00	0.73 (0.42, 1.28)	0.66 (0.37, 1.20)	0.80 (0.40, 1.59)	0.31	
PFCs with BC vs control	1.00	0.91 (0.49, 1.69)	1.17 (0.62, 2.19)	1.35 (0.62, 2.95)	0.38	
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	1.35 (0.67, 2.71)	2.21 (1.11, 4.44)	1.99 (0.88, 4.46)	0.03	
All BCs vs PFCs alone	1.00	1.31 (0.76, 2.25)	1.51 (0.86, 2.67)	1.88 (0.99, 3.57)	0.04	
Linoleic acid (18:2)	$0 < n \le 10.19$	10.19 < n < 11.40	11.40 < n < 13.63	13.63 < n	0.0.	
PFCs alone vs control	1.00	0.70 (0.40, 1.24)	0.60 (0.33, 1.11)	0.88 (0.43, 1.78)	0.40	
PFCs with BC vs control	1.00	0.50 (0.27, 0.92)	0.47 (0.25, 0.91)	0.73 (0.33, 1.61)	0.13	
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	0.83 (0.43, 1.60)	0.84 (0.40, 1.76)	0.92 (0.42, 2.02)	0.75	
All BCs vs PFCs alone	1.00	1.05 (0.62, 1.80)	1.04 (0.58, 1.89)	1.17 (0.62, 2.19)	0.67	
2-Linolenic acid (18:3n–6)	$0 < n \le 0.05$	$0.05 < n \le 0.07$	$0.07 < n \le 0.09$	0.09 < n	—	
PFCs alone vs control	1.00	$0.68 \ (0.40, 1.15)$	$1.17 \ (0.59, 2.31)$	1.03 (0.52, 2.04)	0.72	
PFCs with BC vs control	1.00	1.15 (0.61, 2.16)	2.57 (1.24, 5.32)	2.54 (1.19, 5.42)	0.003	
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	1.74 (0.88, 3.42)	2.28 (1.04, 5.01)	2.50 (1.13, 5.57)	0.003	
All BCs vs PFCs alone	1.00	1.32 (0.78, 2.26)	1.59 (0.85, 3.00)	2.23 (1.22, 4.07)	0.008	
Arachidonic acid (20:4)	$0 < n \le 11.43$	` ' '	$12.17 < n \le 12.92$	12.92 < n	U.008	
PFCs alone vs control	$0 < n \le 11.43$ $1.00$	$11.43 < n \le 12.17$			0.54	
PFCs with BC vs control	1.00	0.93 (0.51, 1.68)	0.77 (0.41, 1.47)	0.86 (0.45, 1.62)	0.34	
2		0.74 (0.36, 1.53) 0.78 (0.36, 1.70)	1.72 (0.88, 3.38)	1.11 (0.56, 2.18) 1.41 (0.67, 3.00)		
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	` ' '	1.84 (0.87, 3.88)	` ' '	0.11	
All BCs vs PFCs alone 1–3 PUFAs <sup>5</sup>	1.00	0.63 (0.35, 1.13)	1.35 (0.75, 2.43)	0.93 (0.51, 1.69)	0.53	
	$0 < n \le 7.05$	$7.05 < n \le 7.64$	$7.64 < n \le 8.36$	8.36 < n		
PFCs alone vs control	1.00	0.61 (0.31, 1.20)	0.92 (0.49, 1.72)	1.04 (0.57, 1.92)	0.57	
PFCs with BC vs control	1.00	0.73 (0.36, 1.46)	0.83 (0.43, 1.59)	0.61 (0.31, 1.20)	0.22	
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	1.51 (0.70, 3.26)	1.19 (0.59, 2.42)	0.76 (0.37, 1.59)	0.37	
All BCs vs PFCs alone	1.00	1.01 (0.55, 1.87)	0.84 (0.47, 1.48)	0.57 (0.32, 1.00)	0.04	
Eicosapentaenoic acid (20:5)	$0 < n \le 0.46$	$0.46 < n \le 0.56$	$0.56 < n \le 0.69$	0.69 < n		
PFCs alone vs control	1.00	0.74 (0.90, 0.47)	1.23 (0.68, 2.21)	0.93 (0.50, 1.74)	0.91	
PFCs with BC vs control	1.00	1.29 (0.68, 2.43)	0.74 (0.39, 1.42)	0.79 (0.40, 1.55)	0.25	
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	1.32 (0.65, 2.67)	0.50 (0.24, 1.05)	0.78 (0.37, 1.65)	0.15	
All BCs vs PFCs alone	1.00	1.15 (0.65, 2.04)	0.48 (0.27, 0.85)	0.51 (0.27, 0.94)	0.003	
Docosapentaenoic acid (22:5)	$0 < n \le 1.62$	$1.62 < n \le 1.85$	$1.85 < n \le 2.09$	2.09 < n	_	
PFCs alone vs control	1.00	0.86 (0.45, 1.63)	0.99 (0.51, 1.93)	1.00 (0.50, 1.98)	0.87	
PFCs with BC vs control	1.00	0.63 (0.30, 1.30)	1.05 (0.51, 2.15)	0.57 (0.27, 1.23)	0.35	
PFCs with BC vs PFC alone <sup>3</sup>	1.00	0.65 (0.31, 1.38)	1.01 (0.49, 2.10)	0.79 (0.37, 1.71)	0.88	
All BCs vs PFCs alone	1.00	0.65 (0.36, 1.17)	0.87 (0.48, 1.57)	0.57 (0.30, 1.08)	0.20	
Docosahexaenoic acid (22:6)	$0 < n \le 4.40$	$4.40 < n \le 4.90$	$4.90 < n \le 5.46$	5.46 < n	_	
PFCs alone vs control	1.00	0.82 (0.41, 1.63)	0.77 (0.40, 1.49)	1.33 (0.72, 2.45)	0.29	

(Continued)

TABLE 4 (Continued)

	1	2	3	4	P for trend
		% of t	otal by wt		
PFCs with BC vs control	1.00	0.80 (0.40, 1.58)	0.68 (0.35, 1.32)	0.81 (0.43, 1.53)	0.47
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	1.05 (0.48, 2.31)	0.96 (0.46, 2.04)	0.72 (0.35, 1.48)	0.32
All BCs vs PFCs alone	1.00	0.86 (0.46, 1.63)	0.84 (0.46, 1.54)	0.58 (0.33, 1.01)	0.06

<sup>&</sup>lt;sup>1</sup> PUFAs, polyunsaturated fatty acids. Models were stratified by year of interview (1995–1996, 1998–1999, and 2000–2001) and adjusted for age by conditional logistic regression analysis. Number of subjects in age-adjusted model: 185 with PFCs, 114 with NPFCs and BC, and 1030 control subjects.

changes as compared with women with PFCs only. Palmitoleic acid was directly associated with risk of PFC and breast cancer with proliferative changes as compared with controls. There were no significant associations for total PUFAs, total monounsaturated fatty acids, stearic acid, α-linolenic acid (18:3n–3), SI (n–9), or erucic acid in any of the models considered (data not shown).

In Table 5 we present results for ratios of fatty acids that show activity of enzymes involved in fatty acid metabolism. The n-7 SI for palmitic to palmitoleic acids was inversely associated with risk in all models considered, although the trend OR did not reach significance for risk of breast cancer with proliferative changes as compared with PFC alone. This finding, both for the proliferative and nonproliferative disease models, was driven primarily by lower concentrations of palmitoleic acid (denominator) with increasing SI quartile rather than changes in palmitic acid (numerator). The n-3:n-6 fatty acid ratio was significantly inversely associated with risk of all breast cancer as compared with PFCs, and a similar although nonsignificant trend was seen for breast cancer with proliferative changes as compared with PFCs. Finally, the ratio of LA to GLA was associated with a significant reduction in risk of all breast cancer as compared with PFCs, of breast cancer with nonproliferative changes and breast cancer with proliferative changes as compared with controls, and of breast cancer with proliferative changes as compared with PFCs alone. The opposite association, a significant increase in risk, was seen for the ratio of GLA to AA.

## DISCUSSION

We observed a significant inverse association between total n-3 fatty acids, more specifically EPA, and risk of NPFCs alone or with concurrent breast cancer, and between risk of breast cancer with or without proliferative changes and PFCs alone. GLA and palmitoleic acid were positively associated with nearly all conditions, whereas palmitic acid was primarily associated with a significant increase in risk of nonproliferative changes in subjects with or without cancer.

Most previous studies of diet and fibrocystic conditions analyzed exposure to various forms of fat through self-reported dietary intake (4–6, 8, 9). One such cohort study of diet among adolescent females enrolled in the Nurses' Health Study II reported a marginally significant positive association between total

monounsaturated fat intake and risk of PFCs (multivariate OR: 1.52; 95% CI: 1.05, 2.21) (4). Early case-control studies suggested a positive association between total fat intake and risk of fibrocystic disease (6, 24). However, later cohort and case-cohort studies reported no association (8, 9). Limitations of these studies were that PUFAs were only reported as a single category, and the role of n–3 fatty acids and n–6 fatty acids was not distinguished.

There have also been studies of breast adipose tissue concentrations of fatty acids in women with breast cancer compared with those with BBD (PFCs, NPFCs, and fibroadenoma) (10–13, 25). In support of our findings, 3 of these 5 studies reported significantly lower concentrations of n–3 fatty acids [including ALA, EPA, and docosahexaenoic acid (DHA, 22:6n–3)] in the breast adipose tissue of breast cancer cases than in that of women with benign disease (10–12). In addition, in a recent cohort study (26), risk of breast cancer declined with increasing levels of the n–7 SI.

The positive association we found between GLA and risk of breast cancer, with or without NPFCs or PFCs, compared with women with only NPFCs or PFCs has not been previously documented. GLA showed tumor-reducing effects in animal models (27) and enhanced the cytotoxicity of some chemotherapeutic compounds (paclitaxel and docetaxel) in cell culture (26, 27). Women with PFCs have up to a 4-fold increased risk of breast cancer (28).

To indirectly assess the possible role of enzyme activity on the risk of breast cancer or fibrocystic disease, we evaluated a number of meaningful fatty acid ratios. Desaturase activity is usually assayed in vitro or in animals by measuring the rate of conversion of radiolabeled precursor fatty acids with their respective products (29). Ethical and practical reasons prevent this method from being adopted in humans; thus, indirect information can be gathered from the analysis of cell membrane lipid composition, which is known to indicate desaturation activities (29). The most commonly reported of these is the n-3:n-6 fatty acid ratio, which may indicate both dietary intake and competitive metabolism by  $\Delta^6$ -desaturase. The n-7 SI for the ratio of palmitic to palmitoleic acid may indirectly indicate the activity of  $\Delta^9$ -desaturase because palmitoleic acid is primarily produced through the desaturation of palmitic acid by  $\Delta^9$ -desaturase. Finally, without supplementation, blood concentrations of GLA primarily indicate variations in the desaturation of LA to GLA by  $\Delta^6$ -desaturase or the desaturation of GLA to AA by  $\Delta^5$ -

<sup>&</sup>lt;sup>2</sup> Odds ratio and 95% CI (all such values).

<sup>&</sup>lt;sup>3</sup> Adjusted for age and number of induced abortions, stratified by year of interview.

 $<sup>^{4}</sup>$  18:2n-6cc + 18:3n-6 + 20:2n-6 + 20:3n-6 + 20:4n-6 + 22:2n-6 + 22:4n-6.

 $<sup>^{5}</sup>$  18:3n-3 + 20:3n-3 + 20:5n-3 + 22:5n-3 + 22:6n-3.

**TABLE 5**Ratios of erythrocyte fatty acid concentrations among women in Shanghai, China, and risk of nonproliferative fibrocystic conditions (NPFCs) and proliferative fibrocystic conditions (PFCs) with or without breast cancer (BC)<sup>I</sup>

	Quartiles of erythrocyte fatty acid concentrations						
	1	2	3	4	P for trend		
	% of total by wt						
n-7 Saturation index (16:0/16:1n-7)			•				
Erythrocyte fatty acid cutoffs	$0 < n \le 77.8$	$77.8 < n \le 112.3$	$112.3 < n \le 141.5$	141.5 < n			
NPFCs alone vs control	1.00	$1.44 (0.77, 2.72)^2$	0.59 (0.29, 12177)	0.49 (0.25, 0.97)	0.002		
NPFCs with BC vs control	1.00	1.12 (0.63, 2.02)	0.35 (0.18, 0.70)	0.21 (0.10, 0.44)	< 0.0001		
NPFCs with BC vs NPFCs alone	1.00	0.69 (0.35, 1.37)	0.52 (0.24, 1.13)	0.44 (0.19, 1.00)	0.03		
PFCs alone vs control	1.00	1.06 (0.55, 2.03)	0.68 (0.35, 1.34)	0.33 (0.17, 0.67)	0.0004		
PFCs with BC vs control	1.00	1.13 (0.59, 2.15)	0.48 (0.23, 0.99)	0.11 (0.04, 0.27)	< 0.0001		
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	1.22 (0.62, 2.39)	0.86 (0.42, 1.79)	0.47 (0.19, 1.20)	0.10		
All BCs vs PFCs alone	1.00	0.96 (0.55, 1.67)	0.62 (0.34, 1.12)	0.52 (0.26, 1.04)	0.02		
Total n-3:n-6 PUFA <sup>4</sup>							
Erythrocyte fatty acid cutoffs	$0 < n \le 0.24$	0.24 < n < 0.27	$0.27 < n \le 0.31$	0.31 < n			
NPFCs alone vs control	1.00	1.16 (0.61, 2.20)	0.83 (0.44, 1.54)	0.68 (0.35, 1.29)	0.12		
NPFCs with BC vs control	1.00	0.92 (0.48, 1.76)	0.73 (0.40, 1.33)	0.63 (0.33, 1.20)	0.12		
NPFCs with BC vs NPFCs alone	1.00	0.76 (0.36, 1.58)	0.81 (0.40, 1.67)	0.75 (0.35, 1.59)	0.52		
PFCs alone vs control	1.00	1.63 (0.80, 3.32)	1.18 (0.60, 2.32)	1.80 (0.93, 3.50)	0.17		
PFCs with BC vs control	1.00	1.29 (0.60, 2.67)	1.23 (0.62, 2.41)	0.78 (0.38, 1.61)	0.45		
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	0.70 (0.31, 1.58)	0.98 (0.46, 2.08)	0.45 (0.20, 0.99)	0.09		
All BCs vs PFCs alone	1.00	0.61 (0.32, 1.17)	0.75 (0.40, 1.39)	0.38 (0.20, 0.71)	0.006		
Linoleic acid:γ-linolenic acid				, , ,			
Erythrocyte fatty acid cutoffs	0 < n < 128.6	128.6 < n < 173.0	173.0 < n < 229.2	229.2 < n			
NPFCs alone vs control	1.00	0.65 (0.32, 1.34)	0.96 (0.50, 1.87)	1.02 (0.53, 1.97)	0.54		
NPFCs with BC vs control	1.00	0.86 (0.47, 1.58)	0.40 (0.21, 0.78)	0.60 (0.32, 1.12)	0.03		
NPFCs with BC vs NPFCs alone	1.00	0.76 (0.36, 1.58)	0.81 (0.40, 1.67)	0.75 (0.35, 1.59)	0.52		
PFCs alone vs control	1.00	0.83 (0.38, 1.81)	0.30 (0.14, 0.67)	0.42 (0.20, 0.87)	0.004		
PFCs with BC vs control	1.00	0.70 (0.36, 1.36)	0.34 (0.17, 0.68)	0.34 (0.17, 0.70)	< 0.001		
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	0.71 (0.34, 1.48)	0.58 (0.27, 1.25)	0.42 (0.20, 0.89)	0.02		
All BCs vs PFCs alone	1.00	0.74 (0.41, 1.34)	0.54 (0.29, 1.00)	0.51 (0.28, 0.90)	0.01		
γ-Linolenic acid:arachidonic acid				, , ,			
Erythrocyte fatty acid cutoffs	0 < n < 0.004	0.004 < n < 0.006	0.006 < n < 0.008	0.008 < n			
NPFCs alone vs control	1.00	0.74 (0.43, 1.28)	0.79 (0.43, 1.44)	1.00 (0.51, 1.96)	0.83		
NPFCs with BC vs control	1.00	1.07 (0.59, 1.94)	1.18 (0.63, 2.21)	1.68 (0.86, 3.28)	0.15		
NPFCs with BC vs NPFCs alone	1.00	1.30 (0.67, 2.56)	1.48 (0.72, 3.05)	2.14 (1.01, 4.53)	0.05		
PFCs alone vs control	1.00	0.88 (0.50, 1.54)	1.21 (0.66, 2.23)	1.01 (0.49, 2.09)	0.70		
PFCs with BC vs control	1.00	1.17 (0.62, 2.21)	1.47 (0.75, 2.90)	2.20 (1.02, 4.72)	0.04		
PFCs with BC vs PFCs alone <sup>3</sup>	1.00	1.20 (0.61, 2.39)	1.42 (0.68, 2.95)	1.95 (0.87, 4.38)	0.10		
All BCs vs PFCs alone	1.00	1.08 (0.62, 1.88)	1.15 (0.64, 2.05)	2.08 (1.10, 3.91)	0.04		

<sup>&</sup>lt;sup>1</sup> Models were stratified by year of interview (1995–1996, 1998–1999, and 2000–2001) and adjusted for age by conditional logistic regression. Number of subjects in age-adjusted model: 185 with PFCs, 114 with NPFCs and BC, and 1030 control subjects.

desaturase. To indirectly evaluate the effects of the activity of these 2 enzymes on risk, we evaluated the association between the ratios of LA to GLA and of GLA to AA.

Therefore, our finding of an inverse association between the n–7 SI and the risk of both breast cancer and fibrocystic disease with or without proliferation provides indirect evidence that  $\Delta^9$ -desaturase activity may play a role in both the development of fibrocystic changes and their progression to breast cancer. Our findings that the risk of most breast conditions considered decreased as LA increased in relation to GLA (reduced  $\Delta^6$ -desaturase activity) and that the risk of most conditions evaluated increased as GLA increased in relation to AA (reduced  $\Delta^5$ -desaturase activity) suggest a potential role for variations in  $\Delta^6$ - and  $\Delta^5$ -desaturase activity in the development of malignant and nonmalignant breast disease. A

potential impact of reduced desaturase activity may be a reduced ability to inhibit fatty acid synthase gene expression (30). Over-expression of fatty acid synthase was identified in breast cancer tissue and cell lines (31, 32). These findings suggest that direct investigation of the role of desaturase enzymes in the development of fibrocystic disease and breast cancer might be fruitful.

A concern of previous studies of risk factors for BBDs was the potential for bias in case identification. If health-conscious women have a diet different from that of other women and if they are more inclined to seek care for a breast lump than are less health-conscious women, dietary factors and breast diseases could be falsely associated. In the current study, this could only have occurred in the women in the control group of the BSE trial; all women in the intervention arm practiced regular BSE

<sup>&</sup>lt;sup>2</sup> Odds ratio and 95% CI (all such values).

<sup>&</sup>lt;sup>3</sup> Adjusted for age and number of induced abortions, stratified by year of interview.

<sup>&</sup>lt;sup>4</sup> Ratio of n-3 to n-6 polyunsaturated fatty acids.

under supervision of a medical worker and had a follow-up evaluation of all detected lumps by a clinician. Although more breast lumps were detected in the intervention group (14), suggesting that some were missed in the control group, it is unlikely that the rate of detection in this group varied by diet or other lifestyle factors. In addition, control of the analyses for the study arm did not affect the direction or magnitude of our findings. The comparable histologic classification of benign breast lesions and extratumoral tissue in the women with breast cancer was a strength of our study.

Erythrocyte fatty acid concentrations indicate recent dietary intake (approximately the past 3 mo) and thus may not accurately indicate intakes at the time of initiation of fibrocystic or carcinogenic changes. There has been a recent Westernization of the Chinese diet, with an increase in meat consumption. However, these changes may have been less prominent among the older women who were part of these analyses. In addition, changes in dietary intake, absorption, or metabolism due to the presence of BBD or breast cancer could alter erythrocyte fatty acid concentrations in women with this disease. However, the women in the present study were largely asymptomatic at the time of diagnosis and therefore were not likely to have made dietary changes in response to disease.

Another concern is that erythrocyte fatty acids provide only a proxy for the fatty acid composition of the target tissue—the mammary epithelium. However, it has been well documented that changes in dietary intake of long-chain fatty acids, specifically EPA and DHA, are manifested by changes in tissue concentrations throughout the body, and these changes correlate with changes seen in erythrocyte fatty acid concentrations (33).

Many eligible women were excluded from our study, primarily because of inadequate tissue for histologic review. To address this potential source of bias, we compared the breast cancer cases with adequate extratumoral tissue with all other breast cancer cases in the cohort who were diagnosed during the same time period. Women in the study were younger at diagnosis than those not included. Because of the change in childbearing practices during the past 3 decades in China, these younger women also tended to have fewer live births, to be older at first live birth, and to be younger at menarche than older women. This is unlikely to have influenced our results, however, because all of the OR estimates were adjusted for age. Women with fibrocystic breast conditions included in our study were similarly compared with women diagnosed with fibrocystic breast conditions during the period of our present study who were not included. No differences were found (22). Only 40 control women (3.7%) were excluded from the analyses because of an inadequate blood sample; thus, the likelihood of bias as a result of this exclusion is small. The overall response rate of 74.6% in controls was reasonably high.

Only a small number of the women with proliferative fibrocystic changes were determined to have atypia. Although their risk of invasive disease is ≈2 times that of women with proliferative changes without atypia (28), these women were combined with all women with proliferative fibrocystic changes in our analyses because there were insufficient numbers for separate analysis. Finally, although we performed a large number of statistical analyses, which increased the possibility of a chance finding, they were performed to test a priori hypotheses. We have therefore chosen not to use a Bonferroni or similar

correction because this is not common practice in publications of dietary risk factors, particularly when addressing a priori hypotheses.

In summary, our results support a protective effect of total n–3 PUFAs, specifically EPA, and a reduced risk of NPFCs with or without concurrent cancer and risk of breast cancer as compared with PFCs alone. We also provided evidence that high concentrations of palmitoleic acid may increase the risk of both NPFCs and PFCs and the risk of breast cancer in women with NPFCs. However, the ratio of palmitic to palmitoleic acid (n–7 SI) was associated with a reduced risk of all conditions considered, which suggested that the activity of  $\Delta^9$ -desaturase may be of greater importance than individual fatty acid concentrations. Finally, to our knowledge, we are the first investigators to report positive associations between erythrocyte concentrations of GLA and risk of NPFCs, PFCs, and breast cancer. These findings should be viewed with caution until they are reproduced by others.

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